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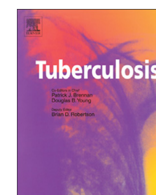

REVIEW

Iron acquisition strategies in mycobacteria

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SUMMARY

Iron is an essential element to most life forms including mycobacterial species. However, in the oxidative atmosphere iron exists as insoluble salts. Free and soluble iron ions are scarce in both the extracellular and intracellular environment which makes iron assimilation very challenging to mycobacteria. Tuberculosis, caused by the pathogen, *Mycobacterium tuberculosis*, is one of the most infectious and deadly diseases in the world. Extensive studies regarding iron acquisition strategies have been documented in mycobacteria, including work on the mycobacterial iron chelators (siderophores), the iron-responsive regulon, and iron transport and utilization pathways. Under low iron conditions, expressions of the genes encoding iron importers, exporters and siderophore biosynthetic enzymes are up-regulated significantly increasing the ability of the bacteria to acquire limited host iron. Disabling these proteins impairs the growth of mycobacteria under low iron conditions both *in vitro* and *in vivo*, and that of pathogenic mycobacteria in animal models. Drugs targeting siderophore-mediated iron transport could offer promising therapeutic options. However, the discovery and characterization of an alternative iron acquisition mechanism, the heme transport and utilization pathway, questions the effectiveness of the siderophore-centered therapeutic strategy. Links have been found between these two distinct iron acquisition mechanisms, thus, targeting a few candidate proteins or mechanisms may influence both pathways, leading to effective elimination of the bacteria in the host.

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1. Introduction

Mycobacteria, like most other living organisms, require iron for many vital functions. Iron forms the essential catalytic centre of the active site of various enzymes enabling enzymatic reactions. The ability of iron to receive and donate an electron thereby oscillating between the ferrous (Fe^{2+}) and ferric (Fe^{3+}) oxidative states enables the enzyme to catalyse redox reactions. For this reason, iron is often associated with cytochromes responsible for oxidative phosphorylation and energy production [1]. Iron–sulfur clusters are essential cofactors of many enzymes involved in amino acid and pyrimidine biogenesis, the tricarboxylic acid cycle as well as electron transport [2]. Iron is one of the most abundant elements on earth, however, under the earth's oxidizing environment at physiological pH, iron exists predominantly as insoluble ferric salts such as iron oxide, iron hydroxide and iron phosphate which cannot be assimilated by bacteria. Free iron ions are therefore scarce. Iron acquisition is even more challenging for pathogenic bacteria because iron ions are bound to host iron-binding proteins, such as transferrin and lactoferrin which serve as host iron transporters, the iron storage protein ferritin and iron-protoporphyrins in hemoproteins [3]. During infection, the host restricts the amount of circulating transferrin-bound iron in the body and reduces the uptake of dietary iron utilising iron-deprivation as a host antimicrobial defense mechanism [4–6]. Pathogenic mycobacteria are, however, able to cause disease despite the severely iron limited host environment. To overcome iron-deprivation mycobacterial pathogens have evolved iron acquiring pathways which are more efficient than those of their vertebrate hosts. In this review, the

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strategies mycobacteria use to access iron and the iron-dependent gene regulation responsible for the maintenance of iron homeostasis in mycobacteria are discussed. Additionally, a brief opinion is given regarding the selection of iron acquisition machineries as drug targets.

2. Siderophore-mediated iron acquisition

A major mechanism employed by mycobacteria to compete for the limited available iron is the use of high affinity iron chelators, siderophores, which are predominantly produced during iron deprivation [7]. There are three types of siderophores, mycobactin, carboxymycobactin and exochelin, where mycobactin and carboxymycobactin share a core structure which is distinct from exochelin. Mycobactin is cell envelope-associated and facilitates the transport of iron through the cell envelope into the cytoplasm while carboxymycobactin and exochelin are secreted iron-chelators which acquire iron in the extracellular milieu and transport iron into the cytoplasm of the bacteria [7].

2.1. The siderophores: mycobactin, carboxymycobactin and exochelin

Mycobactins can be isolated from almost all mycobacterial species except *Mycobacterium microti* [8], *Mycobacterium paratuberculosis*, and *Mycobacterium vaccae* [9]. They have a core structure comprising 5 amino acids with a characteristic phenyloxazolidine ring derived from salicylate with saturated or unsaturated alkyl side chains of various lengths on the hydroxylated lysine residue at the centre of the molecule [10] (Figure 1 and Figure 2a). The long alkyl chain confers the lipophilic property of mycobactin and thereby locates it within the cell envelope [7].

Early studies created confusion by using the term “exochelin” to describe all extracellular siderophores isolated from both saprophytic and pathogenic mycobacteria. This became inappropriate when “exochelin” from pathogenic mycobacteria was found to have a different core structure from that of saprophytic mycobacteria. The former has a core structure similar to that of mycobactin, but with shorter alkyl side chains that terminate with either a carboxyl group or a methyl ester (Figure 2b) [12,13]. This feature makes these “exochelin” molecules more hydrophilic than the lipophilic mycobactins. These molecules were renamed carboxymycobactin [14], although less frequently “exomycobactin” is used.

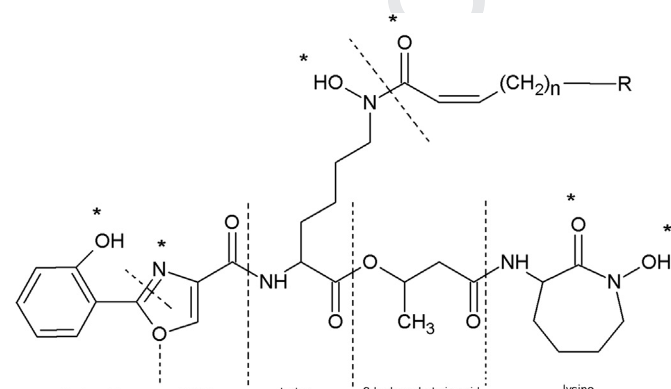

Figure 1. The general structure of mycobactin from *M. tuberculosis*. The structure consists of 5 amino acids including one salicylic acid, one serine, two lysines, and one 3-hydroxybutyric acid. A long alkyl chain extends from the side chain of the middle lysine residue where the length of the R-group may vary amongst the mycobacteria species. The asterisk (*) indicates the chelating group for the ferric ion binding [6]. Copyright (2004) Elsevier, license number for the permission of reuse: 3451920576018.

The extracellular siderophores from saprophytic mycobacteria retained the name exochelin. This water-soluble molecule has a different core structure to mycobactin/carboxymycobactin. consisting of a formylated pentapeptide: *N*-(δ-*N*-formayl, δ-*N*-hydroxy-R-ornithyl)-βalaninyl-δ-*N*-hydroxy-R-ornithinyl-*R*-allo-threoninyl-δ-*N*-hydroxy-S-ornithine (Figure 2c) [15]. The two peptide bonds within the molecule are atypical making them resistant to peptidase hydrolysis. The structure of exochelin varies in some mycobacterial species, e.g. in *Mycobacterium neoaurum* exochelin is a hexapeptide with an unusual β-hydroxyhistidine residue [16].

Carboxymycobactin was thought to be exclusive to pathogenic mycobacteria until it was found to comprise about 5% of the total siderophore content in *Mycobacterium smegmatis* [14]. The coexistence of carboxymycobactin and exochelin in *M. smegmatis* further assisted in resolving the historical confusion between the two siderophores. The difference in core structure of mycobactin/carboxymycobactin and exochelin necessitates distinctive biosynthetic pathways and transport mechanisms for the two unrelated siderophores. The identification of the two biosynthetic pathways further clarified the distinction between the two types of siderophores. The machinery for mycobactin biosynthesis is encoded in two gene clusters, *mbtA-J* [17] and *mbtK-N* [18] in both *Mycobacterium tuberculosis* and *M. smegmatis*. The enzymes responsible for exochelin biosynthesis are encoded by *fxbA*, *fxbB* and *fxbC* genes in *M. smegmatis* [19–21]. The biosynthetic pathways of the mycobactin [22,23] and exochelin [21] are described in detail elsewhere.

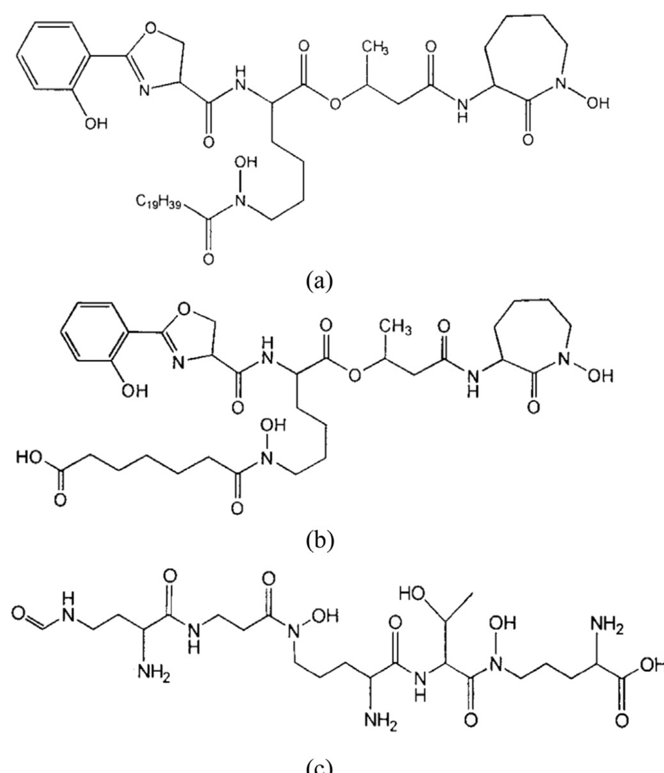

Figure 2. Examples of mycobacterial siderophores. *M. tuberculosis* mycobactin (a) and carboxymycobactin (exomycobactin) structures contain a typical phenyloxazolidine ring (b); The difference between the two molecules is that the *N*-acyl chain on the hydroxylated lysine is a 19-carbon alkyl group (a) while that of carboxymycobactin is a 6-carbon alkyl group coupled with a carboxylic acid (b) [11]. *M. smegmatis* exochelin structure containing 5 amino acids connected with 2 unusual peptide bonds (c) [7]. Copyright (2000) National Academy of Science, U.S.A.

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